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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,502	01/03/2005	Christopher M Ward	021911.001110US	2720
20350	7590	12/13/2006	EXAMINER	
TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			NOBLE, MARCIA STEPHENS	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 12/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/520,502	WARD ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6,8-10 and 14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,8-10 and 14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 October 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

1. Claims 1-6, 8-10, and 14 are pending. Claims 7 and 11-13 are canceled and claims 1, 2, 9, and 14 are amended in Applicant's Response, filed 8/30/2006. Claims 1-6, 8-10, and 14 are under consideration.

Information Disclosure Statement

2. Applicant indicates that they understand that Examiner is not considering the listing of references on pages 67-71 unless the references are present in an IDS. Applicant prefers to retain the list of references in the specification, and this is not improper. Therefore, the objection is withdrawn.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant requests to hold this requirement in abeyance pending determination of the final language of the claims during prosecution. Request to hold this requirement in abeyance is grant with the objection maintained and the requirement to be addressed when the final claim language is determined.

The disclosure, objected to because it contains an embedded hyperlink and/or other form of browser-executable code, had been amended to remove the hyperlinks by

the amendment to the specification, filed 8/30/2006. Therefore, the objection is withdrawn.

Drawings

4. The drawings, objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description, have been amended to include 22a and 22b and clarify the drawings of Figures 16, 17b&c, 22a&b, and 24-27, in amendment filed 8/30/2006 & 10/3/2006. Therefore this objection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6, 8-10, and 14 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising detecting the presences of 5T4 antigen in mouse embryonic stem (mES) cells or human embryonic carcinoma (hEC) cells comprising incubating a sample of mES cells or hEC cells with a labeled anti-5T4 antibody such that specific binding of the antibody to 5T4 cell surface antigen on mouse ES cells or hEC cells occurs and detecting and sorting of mES cells or hEC cells on the basis of presence or absence of 5T4 antibody following the incubation, does not reasonably provide enablement for a method of detecting the

Art Unit: 1632

differentiation status of any stem cell comprising detecting the presence or absence of 5T4 antibody on the surface stem cells wherein the presence of 5T4 antigen represents stem cells in a more differentiated state and the absence of 5T4 antigen identifies undifferentiated or pluripotent stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant traverses this rejection for several reasons.

First, Applicant states that the standards for rejection under 112, 1st paragraph requires objective reasoning to doubt the presumption of an enabling disclosure and mere reliance on assertions of possibilities or conjectures are not enough. They state that there must be objective reasons why undue experimentation is necessary to make and use the claimed invention. These statements imply that Examiner did not make objective arguments and relied upon possibilities and conjecture.

It is acknowledged that the reasons provided in the enablement rejection were based upon reasoning and did not provided art to support these arguments. However, as stated in MPEP § 2164.04, "the minimal requirement is for the examiner to give reasoning for the uncertainty of enablement...References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required." In the instant rejection of record, Examiner presented a *prima facie* case of lack on enablement bases on fact well established in the art and logical reasoning that can be deduced from these fact well established in the art. Therefore, Examiner provides objective reasoning for the lack of enablement rejection.

Second, Applicant states that the rejection alleges that incorporation of mES cells into chimera is not a measure of differentiation that that 5T4 antigen has not been demonstrated as a definitive marker of stem cells. Applicant traverses this argument on the grounds that Examiner misunderstood the nature of the experiment and its possible interpretations. Applicant states that mES cells are known to be able to contribute to functional germ line chimeras and ES cell descendants are known to be represented among all cell types in resulting chimeric offspring. Applicant also stated that Examiner misinterpreted to the experimental data and that it is inaccurate to interpret the results, were 48% of the 5T4 negative cell population did not incorporate into chimers as demonstrating that 5T4 negative cells are not pluripotent and the chimeric generation is inefficient for various factors. Applicant states that the disclosed experiments are directed to the relationship between the absence of 5T4 expression and pluripotency compared to the presence of 5T4 expression and the lack of pluripotency and then point to the co-expression patterns with SSEA, an established stem cell marker.

These arguments are not found persuasive to overcome the instant enablement rejection. The ground of rejection was based on the fact that the incorporation of 5T4 positive ES cells in a chimera does not measure pluripotency or differentiation status. As previously stated in the Non-Final rejection, it is well established that by the definition, the true test of a stem cell is to demonstrate that the stem cells can become any tissue or multiple tissues. It is acknowledged that if a stem cell is present in a chimera, it can contribute to various tissues in the chimera by the process of differentiation. However, to determine if a cell has contributed to the generation of

Art Unit: 1632

various tissue types, one must track the suspected stem cell through the differentiation process by determining if it first starts off as the ES cell type and that specific cell type becomes another cell type of several tissue lineages in the chimeric animal. This tracking the suspected ES cells and their differentiation status and outcome was not established. The mere incorporation of a cell into a chimera does not identify more than the fact that the cell survived and is now a part of the chimeric animal. Therefore, this is the reasoning as to why the formation of a chimera in itself with suspected ES cell is not a test of differentiation. Examiner's discussion of the 48% of the negative cell not incorporating into chimera was meant to further demonstrate that the fate and differentiation status is not clear from the chimera experiments and not to state that 5T4 negative cells are definitively not stem cell or undifferentiated, but to demonstrate that chimera experiments in themselves will not demonstrate the differentiation status of a cell. Therefore, from these experiments it is not clear what the differentiation status of the 5T4 positive cells truly are. Applicant also points to correlative data with established SSEA stem cell marker to demonstrate a correlation between 5T4 negative cells have a coexpression pattern similar to SSEA, suggestive of cells in the undifferentiated state. However, just because a protein is not present in the undifferentiated state and is expressed after removal of LIF in culture, does not definitively make it a marker for stem cells. It is an excellent candidate as a marker of differentiation, but until it is demonstrated that ES cell that are negative for 5T4 antigen can differentiate into other cell types and express the 5T4 antigen in the new tissue cell type, 5T4 antigen can not

be considered a marker for differentiation as claimed. The expression patterns for 5T4 antigen are merely descriptive and identify a candidate stem cell marker.

Third, Applicant traverse the ground of rejection that the instantly claimed invention would require undue experimentation to use or make the instant method because an artisan would have to determine if cells identified and isolated by the lack of 5T4 antigen can differentiate into several cell types. Applicant points to example 3 and figure 14b and states on p 12, par 4 of Applicant's response, filed 10/3/2006, "14b shows that following spontaneous differentiation of mES cell in culture, 5T4 is expressed in all three primary germ layers derived from the stem cell....Seepage 58, lines 20-27." This is not an accurate assessment of these data and disclose. First, the disclosure does not state or show spontaneous differentiation. The discussion in line 17 on page 58 of the specification suggest that "perhaps spontaneously differentiating cells" in reference to a different set of cells that were demonstrating unclear results. In Figure 14b, the experiment cultures different mES cells that were **derived from** different germ layer and determines if the cells express 5T4 antigen when LIF is removed and determine if the cells express transcript associated with differentiation specific to the germ layer from which they were derived after LIF removal (p. 58, lines 20-27). This is not the same as taking totipotent ES cells and differentiating them into different germ layer as suggested by Applicant's response. The mES cells were derived from different embryonic tissues layers and were already to some unknown extent differentiated and not express expressing 5T4 antigen. Then when the LIF was removed they demonstrated the cells, already in some state of differentiation, began to express 5T4

Art Unit: 1632

antigen and again demonstrated the cells cultured in the absence of LIF expressed differentiation markers from the germ layers from which they were derived. Therefore, since the ES cells were already in some unknown state of differentiation because they were derived from early differentiated tissues (i.e.-germ layers), it is not clear what the differentiation state of the cells are before the removal of LIF and continues to unclear how much or if it differs from that following removal of LIF. Therefore, Applicants had not demonstrated that an artisan would not have to determine if the cells not expressing 5T4 are truly undifferentiated cells that can develop into several different cell types, which would be considered the burden of undue experimentation. Therefore, this argument is not found persuasive and the ground of rejection is maintained.

Therefore, since neither the arguments presented by Applicant nor the amendments to the claims have overcome the grounds of rejection. The scope of enablement is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 2 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "low level" in claim 2 still is a relative term which renders the claim indefinite. The term "low level" is not defined by the claim, the specification does not

Art Unit: 1632

provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicant argues that the revision to the claims to recite "a low or negligible expression" clarifies the term.

Examiner does not agree. The addition of the term "negligible" is also a relative term which renders the claim indefinite. The term "negligible" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Overall the question becomes "low or negligible" compared to what. The claims to not have a point of comparison and furthermore if they did, "low or negligible" is at the discretion of the artisan which can vary from one to the other. Therefore, the rejection is maintained.

NEW 112, 2nd Paragraph Rejection

The amendments to the claims necessitate the following new rejection:

7. Claims 1-6 and 14 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 14 now recite "reflects". The metes and bounds of the term "reflect" are indefinite due to the breadth of its interpretation. "Reflect" can be interpreted as to case or show an image, to present a reverse or "mirror" image, to think

Art Unit: 1632

or ponder or even to discredit. Because the meaning of "reflect" can be interpreted greatly, it is unclear if the levels of expression will demonstrate a specific differentiation status or merely ponder a differentiation status.

Claims 2-6 depend from claim 1 which is deemed indefinite. Therefore, dependent claims 2-6 are rendered indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3, 8, and 14 stand rejected under 35 U.S.C. 102(b) as being anticipated by Southall et al (Br J Cancer 61:89-95, 1990). Claims 5 and 6 are removed from the rejection because they were included in error. Therefore the rejection of claims 5 and 6 is withdrawn.

Applicant traversed this rejection on the grounds that the claims are drawn to stem cell and Southall et al encompass carcinoma cell. Applicant states that even if carcinoma cells can be construed as stem cells, the 5T4 positive status in neoplastic cell is indicative of less differentiation, the exact opposite to the situation of stem cells.

Applicant's arguments are not found persuasive. This rejection was intended to demonstrate the breadth of the claims and that it encompasses subject matter not intended in the instant invention. Because the claims are drawn to "any stem cell",

Art Unit: 1632

carcinoma cells can be considered stem cells because most carcinomas are characteristically clonal and undifferentiated, they can be considered stem cells (see abstract, figures 1 and 2 and Tables on pages 91-93) as previously stated in the Non-Final Rejection. Applicant also indicates that the 5T4 is demonstrating a different differentiation status than those intended by the instant invention. However, the claims only state "reflect the differentiation status". The claims do not require a specific differentiation status. Furthermore, the claims recite, "reflect" which could mean that they could mirror a differentiation status, be similar to a differentiation status, or even just thought of as some type of differentiation status. Therefore because the arguments and the amendments do not overcome the instant rejection, the rejection is maintained.

9. Claims 9 and 10, rejected under 35 U.S.C. 102(b) as being anticipated by Boyle et al (Hum Genet 84:455-458, 1990), have been amended and are no longer anticipated by the instant art. Therefore, the rejection is withdrawn.

Applicant traversed this rejection on the grounds that the Boyle et al does not disclose "from a mixture of differentiated and undifferentiated stem cells" as the amendments to the claims require.

Applicant's arguments are found persuasive and therefore the rejection is withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

Art Unit: 1632

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1632

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1632


ANNE-MARIE FALK, PH.D
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